THE EFFECT OF AN ACUTE INFUSION OF VINCAMINE AND ETHYL APOVINCAMINATE ON CEREBRAL BLOOD FLOW IN HEALTHY VOLUNTEERS

The Vinca alkaloid vincamine has been reported to increase cerebral blood flow (Kohlmeyer, 1977) and is widely used in Europe as a treatment for cerebrovascular disorders. Recently the apo-ester derivative ethyl apovincaminate (EAV) has been put forward as an alternative treatment (Solit, Iskum & Czako, 1976; Orosz, Déak & Benoist, 1976). We therefore designed a small study to compare the acute effect of the two drugs on cerebral blood flow.

We studied six healthy male volunteers aged 25–47 years who had given informed consent to the study. No medication was allowed for 2 weeks before or during the study. Each subject received a weekly 20 min infusion of 5% dextrose containing either vincamine 40 mg, ethyl apovincaminate 20 mg or a placebo injection containing the excipients alone, according to a double-blind, balanced, randomized, cross over design covering a three week period. Supine cerebral blood flow measured by the 2 min radioactive Xenon technique (Wyper, Lennox & Rowan, 1976), expired CO_2 concentration, blood pressure and pulse were measured at 0, 10 and 20 min on each occasion.

The means of the cerebral blood flow (CBF) results are shown in Table 1. A small but significant fall occurred during the placebo infusion (paired t-test, $P = < 0.02$). The mean difference ($\pm$s.e. mean) between the changes in CBF during the placebo and drug infusion was greatest during the second half of the infusion period and was $+4 \pm 2$ ml 100 g^{-1} min^{-1} ($+9\%$) for vincamine and $+3 \pm 2$ ml 100 g^{-1} min^{-1} ($+7\%$) for ethyl apovincaminate but these changes were not significant. A significant fall in mean pulse rate ($+$s.e. mean) occurred during the infusion of vincamine (-10 ± 3 beats/min, $P = < 0.05$) and ethyl apovincaminate (-8 ± 3 beats/min, $P = < 0.05$) but not placebo (-1 ± 2 beats/min).

Five of the six volunteers spontaneously complained of symptoms with at least one of the drugs. Three subjects complained of tinnitus during the infusion of vincamine. Two subjects developed dizziness and faintness on standing after the infusion (one, vincamine; one, ethyl apovincaminate). One subject developed mild facial flushing (ethyl apovincaminate) and one thrombosis of an arm vein (vincamine). No subject developed symptoms with placebo.

A small fall in CBF following dextrose infusion in the supine position has been noted previously in this laboratory. After allowing for this we found a small rise in CBF during the second half of the infusion of both drugs but this change was not significant. Any change might be minimized by effective autoregulation. In an uncontrolled study using intracarotid injection of ^{133}Xe in elderly subjects with cerebrovascular disease (Kohlmeyer, 1977) 30 mg vincamine i.v. produced a significant increase ($+12\%$) in mean CBF. We were unable to confirm that either drug produces useful changes in the CBF of healthy subjects and the side effects of bradycardia, faintness and tinnitus would seem to contraindicate their routine use until further studies have been done to confirm their safety and efficacy in elderly subjects.

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Table 1 Mean cerebral flow $\pm$ s.e. mean (ml 100 g^{-1} min^{-1}) and mean estimated arterial p CO_2 in brackets (mm Hg) of six subjects.

	Time (min)		
	0	*10*	*20*
Ethyl apovincaminate	45 ± 2 (38)	43 ± 2 (39)	44 ± 3 (38)
Vincamine	46 ± 2 (39)	45 ± 3 (39)	44 ± 3 (40)
Placebo	47 ± 2 (40)	46 ± 3 (40)	43 ± 2 (41)

References

KOHLMEYER, K. (1977). Zur Wirkung von Vincamin auf die Gehirdurchblutung des Menschen im Akutversuch. *Arzneim-Forsch., (Drug Res)*, **27**, 6A 1285–1290.

OROSZ, É., DÉAK, Gy. & BENOIST, Gy. (1976). Effect of Ethyl apovincaminate on the cerebral circulation. *Arzneim-Forsch.*, (Drug Res), **26**, 10A 1951–1956.

SOLTI, F., ISKUM, M. & CZAKO, E. (1976). Effect of Ethyl apovincaminate on the cerebral circulation. *Arzneim-Forsch.*, (Drug Res.), **26**, 10A 1945–1947.

WYPER, D.J., LENNOX, G.A. & ROWAN, J.D. (1976). Two minute slope inhalation technique for CBF measurement in man. *J. Neurol. Neurosurg. Psychiat.*, **39**, 141–151.

STABLE PROSTAGLANDIN ENDOPEROXIDE ANALOGUES AND HUMAN GASTRIC MUCOSAL ADENYLATE CYCLASE

The prostaglandin endoperoxides, PG G_2 and PG H_2, play a pivotal role in the biosynthesis of classical prostaglandins (Hamberg & Samuelsson, 1973) as well as of prostacyclin (Moncada, Gryglewski, Bunting & Vane, 1976). Their recently discovered activities in a variety of tissues suggest that they represent a group of potent, short-lived compounds that have the capacity to modulate target cell activity, perhaps through the regulation of cyclic nucleotides (Gorman, 1975).

Prostaglandins of the E- and I-series which are generated in human gastric mucosa via the cyclooxygenase pathway (Bennett, Stamford & Stockley, 1977) as well as the synthetic analogues of PG E_2 have been shown to depress gastric acid secretion in animals and man (Robert, Nezamis & Phillips, 1967, Classen, Koch, Deishle, Weidenhiller & Demling, 1970, Gerkens, Gerber, Shand & Branch, 1978) and to produce striking inhibition of gastric mucosal ulceration in many animal models (Robert, 1976). The precise mechanism of the antisecretory as well as cytoprotective activities of these molecules is still unknown; in general they have been related to action on the cyclic nucleotide systems.

It is possible that some of the effects previously ascribed to the classical prostaglandins are in fact secondary to actions to prostaglandin endoperoxides, the immediate precursors, so that these compounds may be of physiological importance in human gastric function.

The endoperoxides PG G_2 and PG H_2 are intrinsically highly unstable substances (half-life, $T_{\frac{1}{2}}$, about 5 min in aqueous solution at 37°C and pH 7.4). Because of the extraordinary lability and the consequent difficulties and limitations in experimental use, the synthesis of stable and active analogues was deemed extremely important. U 44069 and U 46619, both stable analogues of PG G_2 and PG H_2, have been shown to behave as close mimics of the natural compounds (Bundy, 1975).

Stomach tissue was obtained by subtotal gastric resection from patients suffering from chronic ulcer

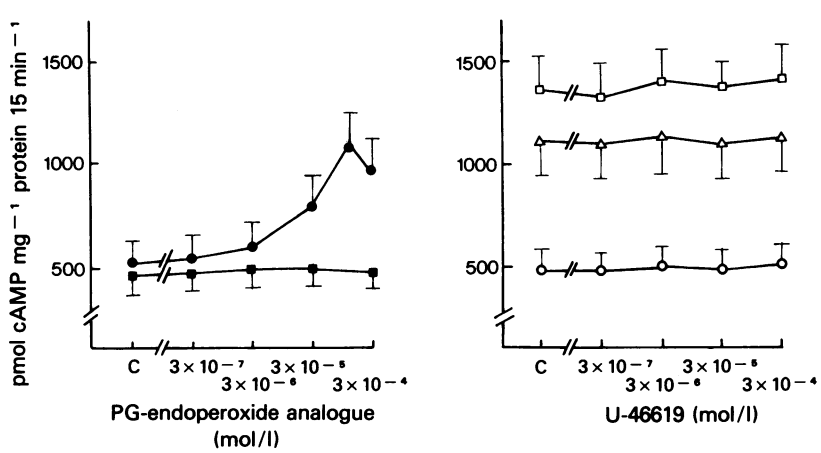

Figure 1 (a) Effect of ascending concentrations of the stable prostaglandin endoperoxide analogues U 44069 (●) and U 46619 (■) upon the adenylate cyclase activity in the corpus region of human gastric mucosa. (b) Effect of increasing concentrations of U 46619 on basal (○), histamine- (△), and NaF (□)-stimulated adenylate cyclase activities in the corpus region of human gastric mucosa. Histamine concentration was 0.5 mmol/l, NaF-concentration was 20 mmol/l.

Both figures show mean ± s.e. mean of six separate experiments, each carried out in triplicate.